Report of the Peer Consultation Meeting on p-Dioxane

Volume I

Submission by
Ferro Corporation, Inc.
for the
Voluntary Children's Chemical Evaluation Program
(VCCEP)

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Erlanger, Kentucky

Peer Consultation Organized by
Toxicology Excellence for Risk Assessment
(http://www.tera.org/peer/)

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NOTE

This report was prepared by scientists of Toxicology Excellence For Risk Assessment (*TERA*) and reviewed by the panel members. The members of the panel served as individuals on this panel, representing their own personal scientific opinions. They did not represent their companies, agencies, funding organizations, or other entities with which they are associated. Their opinions should not be construed to represent the opinions of their employers or those with whom they are affiliated.

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Executive Summary

A panel of scientists with expertise in general toxicology, exposure and risk assessment, physiologically-based pharmacokinetic (PBPK) modeling, genotoxicity, epidemiology, and chemical mode of action met on May 1 and 2, 2007, to conduct a peer consultation of a submission on p-dioxane (CAS No. 123-91-1). The Ferro Corporation, Inc., and its contractor, The Sapphire Group, Inc., prepared the submission for the Voluntary Children's Chemical Evaluation Program (VCCEP). The purpose of the meeting was to provide a science-based forum to discuss whether the existing data are adequate to characterize the risks of p-dioxane to children, and, if not, to identify data needs. The sponsor and authors of the p-dioxane submission provided the panel with summary presentations of the submission's assessments of hazard, exposure, risk characterization, and data needs. The panel discussed the assessments in the submission, together with any additional data that were available to them, and then they identified data needs.

The sponsor explained that p-dioxane was included in the VCCEP pilot because it had been detected in breath samples during the 1980s, and it continues to be detected in air, water, food, and consumer products. Production of p-dioxane was dramatically reduced beginning in 1986, and today U.S. production and use is only a small fraction of what it was in the 1980s. The primary current use is as a process solvent, and Ferro Corporation, Inc. is the sole U.S. producer.

In discussing the hazard assessment, the presenters described results from the existing p-dioxane toxicity studies. They acknowledged that several studies listed in the toxicity tiers of the VCCEP pilot program had not been conducted, especially in the areas of immunotoxicity, reproduction, and development. Rodent drinking water carcinogenicity studies had produced tumors, primarily in hepatic and nasal tissues. The presenters stated that tumors occurred only at high doses, which suggested to them a mode of action consistent with metabolic saturation and cytotoxicity. They said the results also suggested a threshold likely exists for the carcinogenic effect of this chemical.

Several panelists expressed concern regarding the lack of toxicity studies, noting that many of the existing studies were old and of poor quality with insufficient data, particularly in the areas of reproduction and development. Most panel members agreed with the authors that p-dioxane is not genotoxic. They thought a mode of action for cancer that was related to metabolic saturation and cytotoxicity was plausible. They said the existing database could be used to make a stronger case to support a threshold mode of action (MOA) for p-dioxane carcinogenicity, but that the data need to be presented in a more organized fashion, along the lines of the U.S.EPA framework for determining a cancer MOA. Most of the panel believed p-dioxane acted as a cancer promoter and not an initiator, and that liver toxicity was the critical effect; however, some panelists expressed uncertainty regarding these points. Panel members were unsure how to interpret the non-cancer toxicity that occurred at doses below metabolic saturation, and they were troubled by the uncertainty of whether the toxic moiety was the parent molecule or a metabolite. Other panelists said that, in spite of these deficiencies, if substantial decreases in environmental levels and human exposures to p-dioxane were verified and shown to be continuing, the exposures might be low enough to preclude the necessity for conducting further toxicity testing.

In summarizing the exposure assessment, the presenters said that most of the available exposure data on p-dioxane are from the 1980s, but they believed that using these data overestimates the current exposure levels because of the large decrease in production since the 1980s and the corresponding decreases in environmental emissions and human exposures. They noted that environmental releases have decreased 47% in the past 10 years. The presenters listed the sources of p-dioxane from commercial production and noted it is also found in consumer products and in foods. They described its environmental transport and partitioning and explained that potential exposures at steady state are low. The presenters identified several exposure pathways, including ingestion of water, breast milk and food; inhaled air; and dermal contact with water, consumer products and solvents. They presented the mean and 95th percentile daily dose estimates for the populations of interest. They determined that dermal contact is the dominant exposure pathway for production workers and infants, while ingestion is the dominant route of exposure for the other childhood age groups.

Some panel members were concerned that the supply chain of commerce for p-dioxane is not fully known once it leaves the producer, and that all final uses of the chemical might not have been identified. Most panelists were troubled by the lack of recent monitoring data. Some members considered the exposure information to be both outdated and insufficient, and they concluded the sources and fate of p-dioxane were not adequately understood. Local ground water contaminated with chlorinated solvents was a source of concern to some panelists, who noted this issue had not been addressed in the submission. Other members thought the environmental exposure estimates used highly conservative exposure assumptions, and they stated that, in addition to these conservative assumptions, the p-dioxane concentrations in both air and water have been decreasing over time. The panel majority thought that the environmental levels and human exposure data from the 1980s likely over-estimated the current exposures, but many said that more current exposure data were highly desirable.

The presentation on the p-dioxane risk characterization discussed the use of PBPK models and identified several models that had been considered. The presenters described their rationale for deriving an oral reference dose (RfD), a reproductive/developmental RfD, and a reference concentration (RfC). A hazard index (HI) approach was used for both the cancer and the non-cancer endpoints. The authors concluded that no populations of interest are at risk from p-dioxane.

While agreeing in general with the risk characterization approach and the PBPK model used by the sponsors, many members of the panel voiced a variety of reservations about the point of departure (POD) and the uncertainty factors. Several panelists questioned the rationale for some of the uncertainty factors (UFs) used to derive the risk values. The manner in which toxicokinetics information was used also was questioned. A few members of the panel said the risk characterization was sufficiently robust to be applied to all four of the target populations; but others stated that many toxicity studies were either lacking or of poor quality, and both the toxicity and the exposure databases were outdated. Because of these deficiencies, some panelists did not think the risk characterization was adequate.

In summarizing possible data gaps and needs related to the toxicity assessment of p-dioxane, the presenters acknowledged that no immunotoxicity, neurotoxicity, or developmental neurotoxicity studies had been conducted, but they provided reasons why each of these studies might not be necessary, especially in view of the continuing decrease in p-dioxane’s environmental levels and corresponding human exposures. Concerning the exposure assessment, the presenters said obtaining more recent information on occupational exposures and for the p-dioxane content of water, air, food and consumer products were possible data needs. Their opinion was that the data gaps or needs in the toxicology area were of lower priority than those for exposure.

The panel as a whole discussed possible data needs, and then members individually identified their own needs. The majority of panelists favored addressing the need for more current data on exposure before deciding whether additional toxicity testing would be necessary. They wanted refinement of the exposure assessment using more realistic assumptions, and, if necessary, to obtain additional, recent exposure data in areas where it might be needed and have the largest impact. Exposure information that panelists identified for consideration included workplace levels from processing, market basket surveys of finished consumer products, and food, air, and water supplies (including water from contaminated groundwater plumes). Biomonitoring of target populations in order to back-calculate the exposure dose was a need identified by some panelists.

Several panel members identified the rat developmental toxicity and the 2-generation reproduction studies as toxicity data needs, with others identified these studies as data gaps that might become needs depending on the results of additional work in the exposure area. Several panelists thought more pharmacokinetic information or modeling was a data gap or need that could help inform the risk characterization. Several other data needs were identified by single panel members.

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1. Participants

Sponsor

The Ferro Corporation, Inc., Cleveland, Ohio

Presenters

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The Sapphire Group, Inc.

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[1] Panel members served as individuals on this panel, representing their own personal scientific opinions. They did not represent their companies, agencies, funding organizations, or other entities with which they are associated. Their opinions should not be construed to represent the opinions of their employers or those with whom they are affiliated.

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Susan Hunter Youngren, Ph.D. Environmental Biology and Public Policy
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Observers and Other Attendees

A list of observers and other attendees is found in Appendix A.

2. Background

This peer consultation meeting was organized by *TERA*. *TERA* is an independent non-profit organization with a mission to protect public health through the best use of toxicity and exposure information in the development of human health risk assessments. *TERA* has organized and conducted peer review and peer consultation meetings for private and public sponsors since 1996. Under this program, *TERA* is organizing peer consultation meetings for assessments developed as a part of the VCCEP. The p-dioxane assessment was submitted by the Ferro Corporation, Inc.

The VCCEP program is a voluntary pilot program and part of the U.S. Environmental Protection Agency's (EPA) Chemical Right-to-Know Initiative (http://www.epa.gov/chemrtk/vccep/index.htm). The goal of the VCCEP is to enable the public to understand better the potential health risk to children associated with certain chemical exposures. The key question of the program is whether the potential hazards, exposures, and risks to children have been adequately characterized, and, if not, what additional data are necessary. The EPA asked companies that manufacture and/or import 23 chemicals that have been found in human tissues and the environment in various monitoring programs to volunteer to sponsor chemical evaluations in a pilot program. Sponsorship requires the companies to collect or develop health effects and exposure information on their chemicals and then to integrate that information in a risk characterization assessment and a data needs assessment.

The VCCEP pilot program was designed to use a tiered testing approach. For toxicity data, specific types of studies have been assigned to one of three tiers. For exposure data, the depth of exposure information increases with each tier. Tier 1 hazard assessments use all available data, and therefore some of the Tier 1 chemical assessments will include toxicity studies indicated for Tiers 2 or 3. Links to the submission document and appendices are available to the public on the Internet at http://www.tera.org/peer/VCCEP/p-Dioxane/pDioxaneWelcome.html. If data needs are identified through this process, the Ferro Corporation, Inc. will decide whether to volunteer for any additional data generation or testing and whether to provide a Tier 2 assessment for VCCEP peer consultation.

To provide wide-ranging scientific review of the sponsor's assessment, each submission undergoes review and discussion by a peer consultation panel in an open meeting with the public invited to observe. The purpose of the meeting is to provide a science-based peer consultation on the data needs for the chemical, utilizing the assessment submitted by the sponsor, as well as the expertise and knowledge of the panel.

The VCCEP Peer Consultation Panel for the p-dioxane submission consisted of 12 members independently selected by *TERA*. Each panel member disclosed information regarding potential conflicts of interest and biases for the VCCEP program in general, for p-dioxane specifically, and for the Ferro Corporation, Inc. *TERA* evaluated these disclosures in selecting the panel members. The disclosures were publicly presented at the beginning of the meeting (see Appendix B for the panelist disclosure statements). The panel members have experience in various disciplines, including exposure evaluation, risk assessment, PBPK modeling, genotoxicity, epidemiology, and toxicology. The panel received a copy of the submission and the cited references approximately five weeks before the meeting, so that they had adequate time to review the documents and prepare for the discussions. Panel members brought a range of views and perspectives to the peer consultations, reflecting the interest in VCCEP by a wide range of stakeholders. The panel did not attempt to reach consensus, rather the individual opinions of the members are noted. Panel members served as *individuals*, representing their own personal scientific opinions. They did not serve as representatives of their companies, agencies, funding organizations, or other entities with which they are associated. Their opinions should not be construed to represent the opinions of their employers or those with whom they are affiliated.

Members of the public were invited to observe the panel discussions by attending the peer consultation meeting in person or by viewing a live web cast of it. They were also given the opportunity to provide brief oral and written technical comments on the assessment document for the panel's consideration. No public comments were received.

TERA prepared this meeting report. The report summarizes the sponsor's presentations, the panel discussions, the sponsor's comments during the discussions, and any comments from the public. The meeting report is a summary, not a transcript. Individual opinions of the panel members are noted (although panelists are not identified by name), along with areas of agreement and disagreement. Panel members have reviewed the draft report, and their comments, if any, have been incorporated into the final version. The sponsors also were given the opportunity to review the draft report to confirm the accuracy of their presentations and remarks. This report is available on the Internet at http://www.tera.org/peer/VCCEP/p-Dioxane/pDioxaneWelcome.html.

This report is organized into sections corresponding to the submission document: hazard assessment, exposure assessment, risk characterization, and data needs. Issues and concerns raised during the panel discussions did not always lead to recommendations for additional studies or data gathering.

3. Introductions, Conflict of Interest, and Meeting Process

The meeting opened with a welcome by Ms. Jacqueline Patterson of *TERA*. She described the background and purpose of the VCCEP and the agenda for the meeting. Ms. Patterson noted that copies of panel members' biographical sketches and conflict of interest (COI) and bias disclosure statements were provided to all attendees (see Appendix B). All the panel members then introduced themselves and noted whether they had additions or changes in their disclosure statements. Dr. Jayjock informed the panel that he had conducted a risk assessment on p-dioxane approximately 10 to 15 years ago for the

Rohm & Haas Company, when he was their employee, but he did not recall the details or outcome of this assessment.

Dr. Dourson, the panel chair, then described how the meeting would be conducted. He explained that discussions would be based on the items found in the Charge to the Panel (located in Appendix B). He noted that all panelists would have the opportunity to state their own positions on the charge items, to ask one another clarifying questions, and to further discuss the issues. No attempt would be made to reach panel consensus positions on the charge items. The chair reminded the panel that the purpose of the peer consultation is not to critique the submission document *per se*, but to answer questions on data adequacy for characterizing risk to children.

4. Sponsor Introduction

Mr. Alan Olson of the Ferro Corporation, Inc. outlined the presentations to be given during the meeting. (See Appendix C for Mr. Olson's presentation slides, which provide further details.) He noted that p-dioxane was included in the VCCEP pilot program because it had been detected in breath samples in the Total Exposure Assessment Methodology (TEAM) studies (Wallace, 1987), but no biomonitoring of p-dioxane is occurring at the present time. p-Dioxane is known to exist in air, water, food, and consumer products. It currently is used primarily as a process solvent, and Ferro Corporation, Inc. is the sole U.S. producer. Mr. Olson said U.S. production of p-dioxane was dramatically reduced beginning in 1986, and today its U.S. production and use is only a small fraction of what it had been in the early 1980s.

4.1 Clarifying Questions from the Panel

In response to a panelist, Mr. Olson stated that he knew of no biomarkers for p-dioxane exposure and that at least one product containing p-dioxane was listed under California's Proposition 65[2] as a carcinogen, but not as a reproductive toxin. He replied to several other panel member questions as follows: the production decrease that began in 1986 was a steady, gradual decline over many years without spikes occurring in any single years, and the current production of 1-2 million pounds per year is expected to remain steady in the coming years; p-dioxane occurs in consumer products only as an impurity, and its content in foods is *not* derived to any large extent from the cooking process.

5. Hazard Assessment

5.1 Sponsor Presentation

Dr. Michael Gargas and Mr. Richard Hubner of The Sapphire Group, Inc., presented the hazard assessment. (See Appendix C for their presentation slides, which provide further details.) They described the studies listed by EPA for each of the three VCCEP tiers, providing the results of those studies that had been conducted on p-dioxane and noting those studies that had not been conducted. They acknowledged the lack of immunotoxicology testing and stated that few toxicity studies had been conducted in the areas of prenatal development, reproduction, or fertility, although some older studies existed. They noted that rodent drinking water carcinogenicity studies had produced tumors, primarily in hepatic tissue. Nasal tissue tumors also occurred, probably from direct contact of water splashing on the nasal tissues during

[2] Proposition 65's formal title is "The Safe Drinking Water and Toxic Enforcement Act of 1986." It is administered by the California EPA Office of Environmental Health Hazard Assessment (OEHHA) and is intended to promote clean drinking water and keep substances shown to cause cancer and birth defects out of consumer products.

drinking. Some tumors also were observed in mammary glands and testes. The presenters distributed Table 1 from the publication of Stickney et al. (2003) to illustrate their position that the liver and nasal tumors occurred only at high doses, which they said suggests the tumors may have been a consequence of metabolic saturation and resulting cytotoxicity. They added that these data also suggest a threshold exists for the carcinogenic effect in these tissues, although it is not known if the parent compound or a metabolite is responsible for the tumor production. The presenters concluded that the weight of evidence indicates p-dioxane's MOA for cancer is not genotoxicity but is via cytotoxicity occurring after metabolic saturation, followed by cell proliferation and replicative DNA synthesis.

5.2 Clarifying Questions from the Panel

Replying to a question of whether an aldehyde metabolite might be the toxic moiety responsible for the nasal tumors by acting in a manner similar to formaldehyde, Dr. Gargas thought this was unlikely. He said he could not rule it out completely, however, because one of p-dioxane's metabolites is beta-hydroxyethoxy acetaldehyde (HEAA). Dr. Gargas added that the data reported by Yamazaki et al. (1994) suggested a threshold for carcinogenicity, and he inferred from these data that a metabolite was most likely responsible for the hepatic tumors. Asked if HEAA could be used as a biomarker for p-dioxane exposure, Dr. Gargas was not sure, saying that HEAA might result from metabolism of other chemicals besides p-dioxane.

A panelist asked what types of containers were used to administer p-dioxane in the drinking water. Upon learning that a sipper tube rather than an open dish was used, the panelist expressed doubt that direct nasal tissue contact had occurred from splashing while drinking. Another panelist noted that if open dish containers had been used to administer aqueous solutions of the test material, some evaporation of p-dioxane might have occurred and reduced the administered dose. This panelist also wondered if p-dioxane's volatility had been adequately controlled in the *in vitro* genotoxicity assays and if a reduction in the concentration of chemical contacting the test cells might be a reason for the negative mutagenicity results observed in the genotoxicity assays. The partitioning of p-dioxane into the plastic matrices of the assay containers also might have reduced the chemical's concentration in the test solutions and be a cause of the negative results. The presenters had no specific data to refute the possibility that test solutions of p-dioxane might contain less of the chemical then intended, but they stated that p-dioxane's vapor pressure in aqueous solutions is known to be low, and they believed p-dioxane was unlikely to partition from water into the types of plastic used in genotoxicity assay containers. Asked about p-dioxane's volatility when applied to skin, Dr. Gargas replied that the chemical would evaporate from skin if it was not in an aqueous vehicle, but it was less likely to evaporate if applied dermally as an aqueous solution.

Referring to the summary of gene mutation assays presented in Table 4-2 (pages 33-39) of the report, a panelist asked about the amount of spacing between the doses in several of the listed studies and suggested that the individual doses for each genotoxicity study in the report be presented to allow readers to evaluate the dose spacing. This same panelist asked if the database of genotoxicity assays and carcinogenicity studies supporting the proposed MOA for p-dioxane was consistent with the databases supporting similar MOAs proposed for other chemicals. Dr. Gargas answered yes, and he mentioned chloroform as one widely known example in which a similar database had been used to support the same MOA as the sponsor proposed for p-dioxane. Another panel member asked if the sponsors had used a formal framework to investigate and select the most likely MOA for p-dioxane's carcinogenicity, for example, the *Guidelines for Carcinogen Risk Assessment* (U.S.EPA, 2005). Dr. Gargas responded that a formal framework had not been used, but, rather, the proposed MOA for p-dioxane was based upon the existing toxicity test results on the chemical, together with conclusions that several other scientific experts had made about its most likely MOA for carcinogenicity.

5.3 Panel Discussion of the Hazard Assessment

The panel discussion of the hazard assessment addressed these four charge items, which are summarized in the sections that follow:

1. *Discuss whether the available information on acute and chronic toxicity, mode of action, and ADME (absorption, distribution, metabolism, and elimination) are adequate to identify and assess all potential hazards.*

2. *Discuss whether the hazard data are sufficient to identify potential risk for each of these target populations:*
   - *prospective parents*
   - *embryo and fetus*
   - *nursing infants*
   - *post-nursing children through adolescence to the age of sexual maturation*

3. *Discuss whether the data presented adequately support the report's conclusion that p-dioxane is non-genotoxic and requires high, prolonged dosing to produce the tumors observed in animal studies. Also, discuss whether the available data support the report's conclusion that the tumors observed in animal studies occurred only in the presence of cytotoxicity.*

4. *Discuss any other significant issues related to the p-dioxane hazard assessment*

5.3.1 Adequacy of the hazard database and the cancer mode of action (MOA) rationale

Referring to the study by Lane et al. (1982), a panelist noted that, even though the purpose of this study was to evaluate the toxicity of di- and trichloroethane (rather than p-dioxane), it is the only multi-generational or reproduction toxicity study existing on p-dioxane. Therefore, the panelist wondered if the Lane study might be used to identify a No Observed Adverse Effect Level (NOAEL) for developmental or reproductive toxicity of p-dioxane. Another panelist did not think doing this was justified and discounted the Lane study results because the chlorinated chemicals in the administered dosing solution might have affected the metabolism of p-dioxane and thereby altered its toxicity. Dr. Gargas stated he did not think the chlorinated compounds would induce the enzymes responsible for p-dioxane's metabolism or would compete with p-dioxane by competitively binding to the enzymes' receptor sites. However, another panel member had reviewed the Lane study in detail and said the study was flawed for the following reasons: although it stated that females were bred three times and teratology was done on the third litter, the study provided no information on mating procedures; too few litters and only 45-50 fetuses were examined; while no terata were found, the study used only one dose that was too low to see developmental effects, and it employed outdated methodology inappropriate for detecting such effects. This panelist also thought that the study by Giavini et al. (1985) had many problems (e.g., it was poorly documented, used incorrect methodology, and evaluated non-standard parameters of toxicity). In addition, the statistical methods were done incorrectly; resulting in *overly conservative* (i.e., health protective) results. This panelist concluded that the available p-dioxane toxicity data were insufficient to evaluate the potential reproductive or developmental hazards for any of the four target populations. Other panelists agreed that the amount and the quality of developmental and reproductive toxicity information on p-dioxane were much less than desired, but they noted that the environmental levels and human exposures to p-dioxane were continuing to decrease, and they might now be so low as to preclude the necessity for conducting further toxicity testing.

Numerous members of the panel said they were satisfied that the MOA for p-dioxane's carcinogenicity was *not* genotoxicity. However, one of these members noted that no formal framework or criteria for evaluation (e.g., the Hill criteria[3] or the EPA carcinogenicity guidelines [U.S.EPA, 2005]) had been presented to support the proposed MOA for p-dioxane's carcinogenicity. Another reminded the panel that p-dioxane produced non-cancer adverse effects below the reported cytotoxicity levels, and these effects should not be dismissed without explanation.

Several panel members discussed whether the rat nasal tumors were relevant to humans. One of the members described the anatomy and physiology of the rodent upper respiratory system, explaining that it differs from primates by having a nasal septum that inflates to force air into the upper chambers of the nasal cavity and by secreting excess mucus from the nostrils, rather than swallowing it. This panelist thought it was possible that rat nasal tissues were directly contacted by the administered test solution during the process of drinking, even though water bottles with sipper tubes were used. However, the panelist concluded that the nasal tumors observed in the rat study probably were not relevant to humans and cited a publication that provided additional data to support this conclusion (DeSesso, 1993).

The importance of knowing p-dioxane's tissue dosimetry was emphasized by one of the panel members who noted that appropriate dosimetry models could be selected if the dose metric to be used in p-dioxane's risk assessment is known. Unfortunately, it is not known if p-dioxane itself or a metabolite is the toxic moiety; therefore, a PBPK model cannot be developed with any confidence. However, to illustrate how PBPK modeling can be used to determine internal doses of a chemical when the appropriate data are available, this panelist presented a series of slides that had been prepared previously for another project. The slide series presented is titled *Internal Doses of Trihalomethanes in Humans Resulting from Drinking Water Use* (U.S.EPA, 2006) and is provided in Appendix D.) The panelist emphasized that the results of the trihalomethane study are not relevant for p-dioxane because the chemistry of the molecules is so different. The panelist concluded that attempting a similar study on p-dioxane at this time would not add meaningful information because of the limited information currently available on this chemical.

Another member mentioned the publications by Woo and co-workers (Woo et al., 1977, 1978), which showed that administering P450 inducers and inhibitors along with p-dioxane decreased its toxicity, demonstrating that the parent compound is not solely responsible for toxicity and that there may be several activation steps and points of modulation by inducers and inhibitors.

Several panel members discussed the carcinogenicity study by Yamazaki et al. (1994). While noting that this report showed a dose at which liver and nasal tumors were not detectable above background, the members wondered how to interpret the non-cancer toxicity (i.e., *spongiosis hepatis*) reported at doses that were sub-threshold for metabolic saturation. Because none of the panel members were familiar with the term *spongiosis hepatis,* one member searched the toxicology literature for this term during a break in the meeting and reported back to the panel that *spongiosis hepatis* is composed of pericyte cells, which are the cells that surround blood vessels, and *spongiosis hepatis* also is known as "cystic degeneration." Another member said this study's lack of reported statistics on the non-cancer effects raised questions about their significance. Another panelist thought the toxicity data reported in this study might indicate that biologically significant toxicity occurs at relatively low doses below the level of metabolic saturation and that such toxicity might progress to serious effects, including cancer. If this is the case, then precisely identifying the dose levels that result in metabolic saturation might not be needed. Other panelists added that most of the carcinogenicity studies did not find increased tumors incidence at low doses, and the

[3] In 1965, Sir Austin Bradford-Hill, a British medical statistician, established nine criteria to determine the strength of an association between a disease and its supposed causative agent. These criteria routinely are used as a way of determining the causal link between a specific factor and a disease (e.g., in this case, between p-dioxane exposure and cancer).

acute toxicity seen in p-dioxane's short-term studies might be completely unrelated to the cytotoxicity and its sequelae observed in the long-term studies. Other panel members revisited the author's interpretation of the data from Yamazaki et al. (1994), which the authors had taken to indicate that metabolic saturation occurred in the range of 150-250 mg/kg-day. These panelists thought that, based upon the data from all the available p-dioxane toxicity studies, this dose range appeared reasonable for assuming an occurrence of metabolic saturation.

Several panelists noted that knowing the saturation dose range alone, was not sufficient without also knowing the specific toxic moiety, which is needed for extrapolation among species and selection of uncertainty factors. These panelists thought that if the parent molecule is the toxic moiety, then identifying the various metabolites and determining whether they differ among species is less important. However, if the parent molecule is the toxic moiety, it might present an increased hazard *in utero* if the fetus is unable to metabolize it. This may be an important consideration because, while p-dioxane is not known to be teratogenic, its toxicity *in utero* is unknown. Two panelists discussed the amount of information that would be needed to determine whether the parent p-dioxane molecule or a metabolite was responsible for the observed toxicities. They concluded that the amount of data currently available on p-dioxane likely was *not* sufficient.

Other panelists mentioned the lack of hazard data in other areas. The possibility of hormonally mediated effects was identified by one member, who noted the occurrence of ovary and mammary gland tumors in some studies might indicate a hormonal effect. Another member indicated that practically nothing is known about immunotoxicity. A third member said the report appeared to assume that p-dioxane's neurotoxicity was similar to that cause by many other organic solvents, but thought this might not be correct. The panelist cited the study by Kanada et al. (1994) in which oral dosing affected the levels of brain neurotransmitters. Other members were less concerned with the Kanada et al. (1994) report, noting the oral dose was given as a 1,050 mg/kg bolus that was likely high enough to elicit the generalized neurotoxic effects caused by other organic solvent chemicals.

5.3.2 Sufficiency of the hazard data for the target populations

The panel chair summarized the panelists' conclusions for the four target populations identified in Charge Item 2:

> The hazard database supporting *prospective parents* contained several toxicity studies and was considered to be sufficient.
>
> The *embryo and fetus population* were supported only by the study of Giovini et al. (1985). Several short-comings had been identified in this study (see above discussions), and the hazard database for this population was considered to be insufficient.
>
> The two populations of *nursing infants* and *post-nursing children through adolescence to the age of sexual maturation* were supported only by the study of Lane et al. (1982). Several problems had been described for this study (see above discussions), and the hazard database for both of these target populations was considered to be insufficient.

None of the panel members disagreed with this summation.

The epidemiology studies on p-dioxane were described and summarized by one of the panel members. The panelist said the most useful study was that of Buffler et al. (1978), which was a cohort study and specific to p-dioxane. The panelist thought that this study, as well as all the other available epidemiology studies, used insufficient numbers of subjects and lacked sufficient resolving power to be useful. In addition, most of the other studies evaluated the results of exposure to other chemicals together with p-dioxane; therefore, their results were not chemical-specific. The conclusions the panelist drew from the available studies was that most of the studies were negative, and, taken together, insufficient epidemiology data exist to identify cancer as an endpoint of concern for p-dioxane.

6. Exposure Assessment

6.1 Sponsor Presentation

Mr. Richard Stalzer of the Ferro Corporation, Inc., and Mr. Richard Hubner of The Sapphire Group, Inc., presented the exposure assessment. (See Appendix C for their presentation slides, which provide further details.) They said that the high cost of p-dioxane relative to other solvent chemicals has limited its demand during the past several years. Since 1996, the Ferro Corporation, Inc., has been the only U.S. producer of this chemical, half of which it exports to other countries. Most of the available exposure data on p-dioxane date from the 1980s when the chemical was produced in much greater amounts; however, although these data are not recent, the values are conservative because of the large decrease in U.S. production that has occurred since then. Together with the decreased production, environmental releases of p-dioxane have declined, and the 2004 Toxic Chemical Release Inventory (TRI) showed environmental releases down 47% since 1995. The presenters showed slides listing the sources of p-dioxane exposure. They described the chemical's environmental transport and partitioning, the receptor populations, and the exposure pathways. The mean and 95^{th} percentile daily dose estimates also were presented. Dermal contact is the dominant exposure pathway both for workers (because of direct solvent contact) and also for infants (because of contact with body products such as lotions). For the other childhood age groups, the dominant exposure is from ingestion. The presenters stated that all of the exposure estimates relied on conservative approaches, and they noted that doses derived from fugacity modeling were 2 to 4 orders of magnitude lower than media specific and probabilistic forecasts.

6.2 Clarifying Questions from the Panel

Responding to a panelist question, a presenter emphasized that Ferro Corporation's p-dioxane production facility employs less than a dozen production workers, and the company's policy is to transfer any pregnant production workers to non-production jobs; however, no similar policy exists for transferring nursing mothers who might be working on production lines. Another panelist asked about the relative p-dioxane concentrations in infant formula and human milk. Citing the tabular data in Appendix A (page A-28 and A-30), a presenter replied that human milk, even from non-occupationally exposed mothers, would likely contain more p-dioxane than infant formula reconstituted with water that contained average contaminant levels of p-dioxane.

Replying to other panel questions, the presenters said Ferro Corporation does not use p-dioxane as a stabilizer for any chemicals, but some of Ferro's customers might employ p-dioxane for this use. They said the content of p-dioxane as a residual contaminant in final products or the extent to which this content may have changed over the years is not known; however, FDA has a less that 10 ppm limit on p-dioxane impurity in foods and in cosmetics products. The presenters acknowledged the possibility that *non-U.S.-made* p-dioxane and products containing this chemical might enter the U.S. and add to the exposures of U.S. populations.

Some panelists questioned the use of a triangular distribution for almost all of the exposure parameters. The authors said they considered other distributions, but, because of the sparse data available and their assumption of unimodal distribution, they had determined that the triangular distribution was the best to use. A panelist added that such a distribution is conservative compared to lognormal or normal because the thicker tails associated with the triangular distribution means that more area under the curve (probability) is associated with extreme (upper limit) observations.

Panel members questioned the origin and rationale of values contained in the tables of the submission's Appendix A. Mr. Chris Kirman of the Sapphire Group joined the meeting by conference call to answer these questions. Mr. Kirman responded to several panelist questions as follows:

- for the infant dermal exposure calculations occurring from exposure to lotions, he had assumed the entire body surface was covered with lotion, but he used the non-occlusion dermal diffusion coefficient for all of the body; he did not treat the area under the diaper as a separate, occluded body area (as recommended by one of the panelists);
- for the calculated values for infant ingestion exposures, he had assumed the infant drank only human milk from age 0-1 years and drank only water from years 1-2;
- regarding fetal exposure from a mother experiencing occupational exposure, he had assumed the pregnant worker to be exposed for 195 working days (although this would not occur at Ferro Corporation, Inc. because the pregnant worker would be transferred to a non-production job).

6.3 Panel Discussion of the Exposure Assessment

The panel discussion of the exposure assessment addressed seven charge items, and is summarized in the sections that follow.

1. *Discuss whether the fate of p-dioxane is adequately understood, both in the environment and within the human body.*

2. *Are the potential sources of p-dioxane exposure adequately identified? Are there other sources that should have been considered?*

3. *Discuss whether the available data are adequate regarding the following exposure aspects: frequency, duration, and intensity.*

4. *Discuss whether the data, age groupings, parameters, assumptions, and scenarios used in the exposure assessment were appropriate to characterize risk to children. Should other data or scenarios have been evaluated, or should different assumptions have been used?*

5. *Is the combination of monitoring data from the 1980s plus the use of probabilistic modeling sufficient to estimate the <u>current</u> exposures to p-dioxane?*

6. *Discuss whether the estimates of exposure were modeled and calculated correctly.*

7. *Discuss any other significant issues related to the p-dioxane exposure assessment.*

6.3.1 Sources and fate of p-dioxane

Panelists discussed the sources and fate of p-dioxane, and many thought that they are not adequately understood. One noted that the supply chain of commerce for the chemical is not known once it leaves Ferro Corporation, and the final uses are not fully identified. The panelist stated further that the report of the TEAM study (Wallace, 1987) found p-dioxane in exhaled breath 20 years ago, but that information was outdated and insufficient. Several panelists discussed p-dioxane's presence in different types of consumer products (e.g., lacquers, cosmetics) and also in foods. They were not confident that the databases presented to them in the report and its appendix were complete or were recent enough to be relevant to current exposure sources or levels.

Regarding p-dioxane's occurrence and fate in the environment, some members said the environmental exposure estimates appeared to be conservative overall, because the p-dioxane concentration in both air and water would be decreasing over time from decreased production. Other panelists said the greater than 80% reduction in production from the early 1980s, when much of the environmental data were collected, gave them some confidence to assume that a substantial reduction in human exposures likely had occurred over this period, but they could not estimate the amount of this reduction. Another member said that while the average level of individual exposure may be decreasing, the total number of people being exposed might be *increasing* and since there is no recent monitoring, the panel really does not know what is happening with human exposure. This panelist expressed special concern over contaminated local ground water plumes with higher than average p-dioxane content, which might originate from nearby industrial emissions or waste sites where chlorinated solvents have entered the groundwater. The panelist noted that no technology is available to remove p-dioxane from ground water. The presenter responded that the sponsors would accept any reliable new data on the levels of p-dioxane in ground water, including in local water supplies, but the exposure values they had listed in their report were based on the general water data available to them.

6.3.2 Exposure frequency, duration, and intensity and their applications to children

Two panel members thought the sponsor's assessment was conservative (meaning health protective by erring on the side of over-estimating exposure, rather than under-estimating it) in estimating the frequency, duration, and intensity of exposure to p-dioxane. One of these members noted disagreement with the use of triangular distributions, but did not think the distribution would influence the outcome of the exposure assessment in any meaningful way. Another member agreed that that the sponsor's exposure values were conservative for the consumer products, but said the exposure values presented for drinking water did not appear conservative, although they did seem to be reasonable. Several panel members and the presenters discussed the potential "stripping" of p-dioxane from water droplets during personal showering, resulting in inhalation exposure. They noted that effective stripping from aqueous solutions requires vacuum distillation, which would suggest that little would be stripped from routine showering. Several members mentioned there are available models and publications to estimate exposure; however, none of the panel members expressed concern regarding meaningfully increased exposure to p-dioxane from this potential exposure route.

One panel member suggested that the submission might benefit from the exposure assessment presenting data on infants less than 1 year of age drinking reconstituted formula rather than breast milk, and bathing with a bubble bath product containing p-dioxane. The panelist predicted, however, that neither of these additional scenarios would provide exposure values greater than those currently presented for this age group in the submission. (Later in the meeting, to respond to the panelist's comment above on reconstituted formula and breast milk, the sponsors prepared two new tables based on data in Appendix A of their submission and distributed them to the panel. The sponsors said the data in these tables show that concentrations of p-dioxane in breast milk are higher than in formula reconstituted with tap water. See Appendix D for the two tables prepared and distributed by the sponsors.)

6.3.3 Available exposure information; accuracy of calculations and estimations

The majority of panelists stated that the exposure data presented in the submission, which was mostly from the 1980s, likely over-estimated the level of current human exposure, but they were not able to quantify the degree of this over-estimation. Many thought that more current exposure data would help improve confidence in the exposure estimates.

One member suggested that biomonitoring children via their urine or exhaled breath would be helpful, especially if a biomarker specific for p-dioxane exposure were identified, because it could confirm or refute the calculated exposure estimates. A second panelist agreed with doing biomonitoring in order to check the exposure estimates provided in Tables 6-7 and 6-8 (page 150) of the submission. This member also thought that the small margins between the estimated means and 95th percentile doses were less than expected and needed to be confirmed.

7. Risk Characterization

7.1 Sponsor Presentation

Dr. Michael Gargas and Mr. Richard Hubner of The Sapphire Group, Inc., presented the p-dioxane risk characterization. (See Appendix C for their presentation slides, which provide further details.) They discussed the submission's use of PBPK models, citing several publications as the basis of their selection of dose metrics and lactational exposure. They noted that they relied most heavily on the publication of Reitz et al. (1990) in preparing the VCCEP submission; however, since the VCCEP submission was completed, a report (Sweeney and Gargas, 2006) with more recent data for p-dioxane parameterization and validation has become available. (This report had not yet been published at the time of the VCCEP panel meeting, but it was shared with the panel and is included in Appendix D.) The presenters discussed their derivations of a chronic oral RfD and inhalation RfC, as well as a reproductive/developmental RfD for the *in utero* exposure period only. The presenters used a hazard index (HI) approach to characterize risk for both the cancer and the non-cancer endpoints, and they calculated a total HI for the most highly exposed children and most highly exposed pregnant workers. They calculated HIs with both central tendency and upper bound exposure estimates and concluded that the most highly exposed child and pregnant workers are not at risk from these p-dioxane exposures.

7.2 Clarifying Questions From the Panel

In response to some panel members' questions about the reference doses derived for the risk characterization, the presenters said it would not be appropriate to combine the reference doses for inhalation, dermal, and oral exposures because the metabolism of p-dioxane from these routes of exposure would differ as a result of the first-pass liver effects occurring after oral exposure.

The presenters also said that their derivation of a separate RfD specifically for reproduction/development toxicity was acceptable according to an EPA pronouncement from the early 1990s. The reproduction/development RfD of 5.2 mg/kg-day was based upon the study of Giavini et al. (1985) in which slight maternal and embryotoxicity was seen in rats with a NOAEL of 517 mg/kg-day and a total UF of 100. This RfD is intended to protect for *in utero* exposures. .

One panelist noted that the RfC value of 1.1 mg/kg-d presented in slide 6 and also on Table 5-5 on page 123 of the submitted report was in error because the correction factor of 5/7 to account for inhalation exposure duration was not included in the calculation. Dr. Gargas agreed with this comment and said the correct RfC value should be 0.72 mg/kg-d. He added that, because of this corrected RfC value, some other statements in the submitted report would need to be corrected.

7.3 Panel Discussion of the Risk Characterization Assessment

The panel discussion on Risk Characterization addressed four charge items:

1. *For non-cancer endpoints: Although the U.S. EPA has not developed reference values for p-dioxane, other regulatory bodies have. The report presents these existing values and then derives values of its own. Discuss whether the available data support the proposed reference doses presented in the report.*

2. *For cancer endpoints: Discuss whether the risk characterization approach, which used cancer potency factors that assumed a no-threshold response and results from physiologically based pharmacokinetic modeling, is appropriate and adequate for the human target populations (prospective parents, embryo and fetus, nursing infants, post-nursing children).*

3. *Discuss whether the risk characterization adequately characterized the risk for each of these target populations:*
   - *prospective parents*
   - *embryo and fetus*
   - *nursing infant*
   - *post-nursing children through adolescence to the age of sexual maturation.*

4. *Discuss any other significant issues related to the p-dioxane risk characterization.*

7.3.1 Proposed reference doses for non-cancer endpoints

The panel discussed the derivation of the reference doses and reference concentration, and, in particular, the point of departure and the selection of the uncertainty factors.

For the chronic RfD a panel member expressed concern about the significance of the *spongiosis hepatis* effect seen at lower doses than the selected point of departure in the study by Yamazaki, et al. (1994). Another panelist, who had reviewed the Yamazaki study in detail, referred the panel to Table 1 of the study and its accompanying text that discussed *spongiosis hepatis* and liver cancer. This panelist said *spongiosis hepatis* is a toxic effect, but it is *not* a precursor to the hepatocellular cancer associated with p-dioxane. It is a different cell type. The panelist noted that the 30 mg/kg-day intake of p-dioxane from water is below the metabolic saturation point, and no NOAEL for *spongiosis hepatis* was reported in this study.

The selection of uncertainty factors generated significant panel discussion and various opinions. One panelist thought that the manner in which toxicokinetics was used to identify the UF_A (animal-to-human extrapolation) was too questionable to justify replacing the default UF_A value of 10 with the UF_A value of 3 proposed by the sponsors. This panelist also thought that without knowing the correct dose metric for p-dioxane, the UF_D (database uncertainty) should be the default value of 10, rather than the value of 3 proposed by the sponsors. The panelist added that other panel members previously had noted the lack of reliable toxicity studies on p-dioxane, and there is a possibility that the chemical might affect the endocrine system. Another panel member reasoned that since most risk assessors (U.S.EPA, 2002; Dourson, 1994) have considered a five-suite dataset of toxicity studies to be sufficient to avoid the use of *any* UF_D, and since p-dioxane has three studies from this five-suite dataset, a UF_D of 3 rather that the default value of 10 seems appropriate. Other panelists expressed differing opinions on what the UF_D value should be, with one stating that VCCEP's entire focus is on *child-related* effects, so having reliable toxicity studies on these effects in young animals is vital; therefore, the UF_D should be 10. Several others expanded the discussion beyond UF values (which are intended only for *toxicity*) to raise the point that p-dioxane exposure estimates for the target child and prospective parent populations were often overly conservative and, in some cases, the hypothetical worker who was assumed to receive the highest exposure to p-dioxane may not realistically exist. Another panelist pointed out that the primary concern in his opinion was not for pregnant production workers, but rather for consumers ingesting water from p-dioxane-contaminated wells.

One panelist noted that the derivation method used to obtain the RfC value was presented in an unconventional way and therefore raised validity questions.

In response to a question from a presenter on how to compare *subchronic* exposures to *chronic* reference doses in the context of the VCCEP pilot program, the panel chair said that although using chronic reference doses is the most conservative and health protective approach, shorter-term reference doses such as the RfD the sponsor had derived for reproduction/development may also be used. The panel chair added that age-specific information justifies age-specific reference doses, and federal and state agencies routinely use this information in this way when it is available. Another panelist stated that some regulatory agencies use 10% of the lifespan as the critical period of time to justify using a chronic reference dose.

One of the panelists showed a series of slides titled *Interspecies Extrapolation for Non-Cancer Risk Assessment* (these slides are in Appendix D). The slides presented a general PBPK-modeling approach that employed both measured and calculated parameters (animal applied dose, human equivalent applied dose, internal animal and human doses derived from PBPK modeling, and animal and human responses) to achieve interspecies extrapolation. The panelist did not necessarily recommend that the approach presented in the slides be used with p-dioxane.

This same panel member also reviewed the recent report of Sweeney and Gargas (2006) and thought the PBPK model presented in that report was helpful but could be modified to make it more useful for p-dioxane. The Sweeney and Gargas (2006) PBPK model showed good fit at high doses but poor fit at low doses; the difference in fit might be from p-dioxane's induction of enzymes increasing its own metabolism. The panelist was not comfortable using the Sweeney and Gargas model in its present form to replace the default component UF values for p-dioxane.

7.3.2 Use of cancer potency factors that assume no threshold; use of PBPK modeling

Two panel members said that while some data were presented to suggest p-dioxane was a threshold carcinogen, these data were not sufficient to rule out the possibility of a no-threshold MOA. These same members said they supported the sponsor's use of the Reitz et al. (1990) PBPK modeling approach because using an internal dose is better than using some other parameter such as body weight raised to the ¾ power. Since the toxic moiety of p-dioxane is unknown, they reasoned it makes sense to consider both the parent and metabolite; evaluate them both, and use the one that results in the more conservative value, which is essentially what Reitz did. Another member added that if the Reitz model was considered sufficient for addressing the *cancer* endpoint (Charge Item 13), it also should be considered sufficient for addressing the *non-cancer* endpoints (Charge Item 12). None of the panel members disagreed with this statement.

Many panelists thought the sponsors should use the existing database to make a stronger case to support a threshold MOA for p-dioxane carcinogenicity by presenting the information in a more organized manner and following EPA guidance for identifying cancer MOAs. Dr. Gargas noted that the authors had been short of time to meet the VCCEP deadline, but he is very willing to do such revision work in the future.

One panel member said that it does no good to say there is a cancer threshold without knowing where it is, adding that although the reported liver toxicity appears to be the critical effect, it may not be. Another member said that, as a promoter, p-dioxane might be adding to the normal background of carcinogenic events that are constantly occurring in the human population, and it would be good to investigate if and how great this possible addition to the cancer background might be.

7.3.3 Applying the risk characterization to the target populations

Two panelists said substantial deficiencies existed in applying the risk characterization to all four of the target populations, and they noted that, not only are many of the toxicity studies of poor quality, but both the toxicity and exposure databases are very outdated, and more current data are needed. Several other members of the panel emphasized that the exposures to most or all of the target populations had been highly over-estimated in the submission. These over-estimated exposures were great enough to convince one panelist that the risk characterization could be applied to all four populations; however, another member added that just because the exposures were over-estimated does not mean the existing data are adequate to characterize the risk. Another member said the central tendency of exposures to the four populations appears to be known and may have been over-estimated in the submission, but the real concern is with today's *high end* exposures, and these can be obtained through biomonitoring.

8. Data Needs

8.1 Sponsor Presentation

Dr. Richard Hubner and Dr. Michael Gargas of the Sapphire Group, Inc. briefly summarized the information that had been presented and discussed throughout the meeting and related it to possible data gaps or data needs. Concerning the toxicity data, the presenters noted again that no immunotoxicity, neurotoxicity, or developmental neurotoxicity studies had been conducted specifically on p-dioxane; however, they provided numerous reasons why such studies might not be required and why their absence might be considered data gaps rather than data needs. (See Appendix C for the presentation slides, which provide further details.) The presenters said a refinement of the hazard assessment using the Hill Criteria, the EPA cancer guidelines (U.S.EPA, 2005), and the International Program on Chemical Safety Guidance Document (IPCS, 2001) for human relevance also was a possible data gap or data need. In regard to possible data gaps or needs for the exposure assessment, the presenters listed obtaining improved workplace exposure data, survey of water systems affected by chlorinated solvent contamination for potential problems, revisit the TEAM studies and expand to assess current exposure to p-dioxane, and identify and quantify consumer products and foods that may contain p-dioxane. They concluded that the toxicology data gaps are lower in priority than the items listed in the exposure area.

8.2. Clarifying Questions from the Panel

The panelists had no clarifying questions on the data needs presentation.

8.3 Panel Discussion of the Data Needs Assessment

The panel discussion on the Data Needs Assessment addressed two charge items:

1. *Identify any additional hazard information that is needed to be able to adequately characterize risks to children and discuss why it is necessary. Differentiate between data* gaps[4] *and data needs*[5] *. Focus on those studies indicated for the next VCCEP tier*

2. *Identify any additional exposure data or analyses that are needed to be able to adequately characterize risks to children and discuss why this information is necessary for the next VCCEP tier. Differentiate between data gaps and data needs.*

The panel chair explained that in the context of the VCCEP pilot program, *data gaps* are defined as areas that could benefit from additional data, additional studies, additional analysis, or clearer presentation. *Data needs* are defined as data gaps *requiring further work* before the potential risk of the chemical to children can be adequately characterized.

8.3.1 Data needs

The panel chair informed the panelists that because p-dioxane had numerous *data gaps* already identified and acknowledged by the sponsor, the panelists should focus *only* those items which they considered to be *data needs*. The panel chair then requested each individual panel member to identify data needs, after which, the entire panel was invited to discuss the identified data needs.

In deciding what data needs to identify, the panel discussed at length the uncertainty factors that the authors used to derive their chronic RfD, reproductive/developmental RfD, and RfC. A large majority of the panel members believed that the total UF of 100 used by the sponsors was too low; however, they expressed differing opinions on what the appropriate value should be. Two thought a total UF of 100 was justified, while seven others thought the value should be 300, and three thought the UF should be 1000. These differences of opinion were due to various opinions on what each component UF value should be. For the UF_A (animal to human extrapolation) some panel members thought the available information dictated a full value of 10, rather than 3; while others agreed with a UF_A of 3, but thought that the UF_D should be 10. Those panelists suggesting a total UF of 300 said the need for a larger total UF value would depend on whether additional exposure and/or toxicity data were obtained to reduce uncertainty, while one of those suggesting the higher total UF of 1000 maintained that 1000 was needed even if additional data were generated.

Most panelists recommended assigning priorities to the data needs, addressing exposure needs first, and using that information to inform the need for further toxicity information. They said the highest priority is to refine the exposure assessment using more realistic assumptions, and then, if necessary, to obtain additional, recent exposure data in areas where it might be needed (and have the largest impact). Exposure information that panelists identified to consider include workplace levels from processing, market basket surveys of finished consumer products and food, air, and water supplies (including drinking

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[4] In the context of the VCCEP pilot program, *data gaps* are defined as areas that could benefit from additional data, additional analyses, or clearer presentation.

[5] In the context of the VCCEP pilot program, *data needs* are defined as data gaps requiring additional work before the potential risk to children can be adequately characterized. Not all data gaps will be considered data needs. The panelists may consider the risk characterization results when determining whether a data gap is a data need.

water supplies from contaminated plumes). If exposure is low or lower than currently estimated, then additional toxicity data may not be needed. However, other panelists thought that because the exposure data are so uncertain and the available reproductive and developmental toxicity data are so deficient, toxicity studies should be conducted in parallel with the exposure data collection.

Another panel member said that since the overall purpose of VCCEP was to characterize the risk to *children*, the primary data need of this peer consultation meeting was to determine if children are more susceptible to p-dioxane toxicity than adults. Pharmacokinetic data from children or animals, perhaps based on modeling rather than on studies, could help address this area, but the panelist was not identifying this as a specific data need at this time. For example, a juvenile PBPK model could be developed by taking the adult animal model that has been validated in rodents and modifying the model to reflect the human child, and then comparing an internal dose metric for the child with the same dose metric in adults. This might allow adjustment of the UF_H. Another panelist disagreed with using results in this way. Other panelists also said that obtaining additional pharmacokinetic information on children and/or juvenile animals was a data need.

Two panelists identified the rat developmental toxicity and 2-generation reproduction studies as data needs. A third also identified the 2-generation study as a need, adding that kinetic data should be gathered from this study and applied to breast milk exposures, and that an F_1 satellite group should be used to investigate neurotoxicity. Other panelists identified these reproductive and developmental studies as data gaps, but thought that the exposure area should be addressed first to determine if toxicity studies are needed. Some suggested that these two studies might be combined. One of these panelists recommended that, if these studies are done, that an enhanced 1-generation reproductive study or a combined reproductive/developmental screening test (OECD 422 of the Organization for Economic Co-operation and Development Test Guidelines, Federal Register, 2000) be used to reduce the number of animals used.

Biomonitoring of target populations with back-calculations to determine their doses was identified as a data need by three panelists with one member requesting the results be compared to the dose levels associated with the *spongiosis hepatis* finding reported by Yamazaki et al. (1994).

One panelist suggested a multi-step approach to address p-dioxane data needs, suggesting that the first need is for the authors to incorporate into the submission the new PBPK modeling of p-dioxane in rats, mice, and humans (Sweeney and Gargas, 2006), adjusting the dose estimates between rats and humans and revising the RfD, if appropriate. Then current exposure estimates should be compared to the RfD, and, if the HI is greater than 1, then more current exposure data should be gathered and age-specific RfDs should be derived. If the resulting HI is greater than 1, toxicity testing should be done. Several other panel members agreed with this suggestion; however, one member said the uncertainties in the toxicity and exposure databases might preclude a definitive risk assessment, even if PBPK modeling was able to improve extrapolation across species and dose levels.

A number of other data needs were identified by single panel members: the triangular distributions of exposure data replaced by non-parametric presentations; exposure assessments with biomonitoring from p-dioxane-contaminated areas with a focus on pregnant women; determination of the ultimate fate of p-dioxane environmental releases; and requesting the Center for Disease Control and Prevention (CDC) to add p-dioxane to the list of chemicals to be included in the next round of the National Health and Nutrition Examination Survey (NHANES).

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NOTE: The document in Appendix D is the report as it was presented to the panel during the VCCEP peer consultation meeting on May 1-2, 2007. Subsequent to the panel meeting, the report has been submitted for publication and has been accepted pending revision.

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